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TITLE: EPIDEMIOLOGY AND CONTROL OF MALARIA, LEISHMANIASIS  
AND SCHISTOMIASIS

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19. ABSTRACT (Continue on reverse if necessary and identify by block number) Compounds were screened for activity against <i>S. mansoni</i> and data were forwarded to Division of Experimental Therapeutics, WRAIR, for analysis. A new mouse colony was initiated with fresh stock from WRAIR. In leishmaniasis studies, field collections of sandflies were made, and over 3000 sandflies were dissected for species determination and for detection of infections. Three non-leishmanial flagellates were found. Reservoir host studies resulted in a sixth isolate from <i>Proechimys iheringi</i> . It, like the others, was closely related to <i>L. mexicana amazonensis</i> . In a malaria epidemiology project, initial physical examinations were made and medical records initiated on about 1000 people, representing one-third of the population of Costa Marques, and initial mosquitoes survey were made to determine vector species present and to locate breeding sites. Sera were collected to study prevalence of anti-sporozoite antibodies.				
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## FOREWORD

For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

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## PROBLEMS AND OBJECTIVES

Schistosomiasis, malaria and leishmaniasis pose a threat to American military personnel who are or might have to be stationed in the Middle East, Africa, the Far East, the Caribbean or Central and South America. These diseases also inhibit economic development and cause great human misery, a potential source of political unrest in many of the developing countries where they are found. These diseases are highly accessible to study through a cooperative arrangement between the University of Brasilia, Brazil, and the Walter Reed Army Institute of Research.

The mode of transmission of schistosomiasis is such that troops moving through or stationed within endemic areas could be expected to experience a high level of exposure and infection. The distribution of infectious foci is spotty, and there is no way to identify them other than a laborious and detailed search for cercariae in water and/or infected snail hosts. There currently is no single drug that is totally satisfactory for treatment of schistosomiasis. More importantly from the military perspective, there is presently no prophylaxis against the disease. Infected troops, even when treatable, already represent a loss of combat strength and a burden on medical resources. Research on schistosomiasis at this laboratory has the primary objective of detecting, in a primary screening system, compounds with prophylactic and/or therapeutic activity against the disease. A second objective is to maintain access to field study areas with infected human populations and active transmission. These provide an opportunity for testing new anti-schistosomiasis technology and methods for investigating the disease and the biology of its transmission. We have permanent laboratory and living quarters in Caatinga do Moura, Bahia, an area of high endemicity for Schistosoma mansoni.

Malaria is a major and growing public health problem in the Brazilian Amazon. Regional development of agricultural and mineral resources and economic difficulties in the nation as a whole combine to intensify the problem. The reported number of cases has more than quadrupled since 1975, according to Ministry of Health statistics. More than 378,000 cases were reported in 1984, an increase of 27% over the previous

year. Ninety-seven percent of these cases occurred in those states within the Amazon Basin. It is likely that most of the remaining 3% occurred in persons which had visited that region. The quantity and distribution of medical resources in the Amazon, the dispersion of the population and difficulties of transportation mitigate against full reporting. Therefore, what we are seeing is likely a sizeable underestimation of reality. Even so, malaria's impact is conspicuous. The state of Rondonia, in which development is most active, reports more malaria than any other state. Among its population of 731,000 people, 151,140 cases were reported in 1984, equivalent to one case per every five persons per year. Because malaria is unstable in the Amazon, many of these people are acutely ill as adults, and malaria is a major contributor to child mortality.

Control of malaria in the Amazon is complicated by numerous factors, including limited resources, transportation difficulties, the high dispersion of the population and the tendency of people to migrate and remigrate, the rudimentary and open design of housing, drug and insecticide resistance and the behavior of both man and vector. Use of residual DDT as a control method has had limited success. Regular application is often interrupted, because of resource limitations. Many dwellings have only 2 or 3 partial walls. Chloroquine resistance in falciparum malaria has been documented in the Amazon since 1962, and it is no longer used against this species. Fansidar resistance has also been reported. Some populations of the vector are known to be repelled by DDT, neutralizing its effectiveness as a residual control agent. People frequently sit outside their houses during the peak biting time of the vector.

New technology in the form of vaccines and new drugs is critically needed to combat malaria in the Amazon. Field evaluations of new agents require transmission situations that are well understood. The objective of our field malaria work is to provide a well studied population in which new vaccines and/or anti-malarial drugs can be tried. Our approach to this is to evaluate the demographics and the immunological status of the human population in a malarious area, to quantify the dynamics of malaria transmission, including vector studies, and to characterize the malaria strains present. These studies are being conducted in Costa Marques, Rondonia, where we have two houses, one adjacent to the hospital, which we use as a laboratory,

and one for living quarters. Laboratory studies support field work with serology, malaria strain characterization and entomological studies. Entomological laboratory studies include attempts at vector species colonization necessary for vector competence assessments and systematics studies to resolve taxonomic problems.

As far as is known, new world cutaneous leishmaniasis is a sand fly borne disease with wild mammal reservoirs. The number of cases existing in Brazil is unknown. However, in our two study areas, Três Braços and Corte de Pedra, Bahia, over 1000 cases have been treated, 500 in Três Braços over the last 10 years and 500 in Corte de Pedra in the last 18 months alone. The disease is widespread in Brazil, and the mucocutaneous form of the disease, caused by Leishmania braziliensis braziliensis, is frequently encountered in some areas south of the Amazon. The disease is difficult to diagnose in its early stages. Culture for diagnosis and study of some strains of the etiologic agent can not be done reliably. There presently is no way to determine the probability that an infection with L. b. braziliensis will metastasize to the mucocutaneous forms. Therefore, the philosophy of treatment has been that all infections must be treated vigorously. Treatment is painful, of long duration, involves the use of toxic drugs and often has to be repeated because of ineffectiveness and/or relapse. It is not possible to confirm cure with confidence. Recent clinical data indicates that some mucocutaneous patients may go into remission while taking drug treatment but the disease form reappears following termination of treatment. The mucocutaneous form of the disease is potentially hideously disfiguring and may have a fatal outcome. The many days required for therapy and the detailed follow-up required to confirm cure would cause an extreme burden on military medical facilities, if large numbers of troops become infected. The grossly disfiguring effects of advanced mucocutaneous leishmaniasis would horrify and have a negative psychological effect on troops serving in an endemic area, unless they could be given genuine assurance that the disease is preventable or treatable. We are presently unable to prevent this diseases, and the reservoir host(s) and vector(s) of L. b. braziliensis are poorly known. Thus, well focused control strategies can not be implemented against them. It is highly relevant to the development of effective

control methods that the vector(s) and animal reservoir(s) for the disease be identified and studied.

Leishmaniasis research at USAMRU/Brasilia has the objective of determining the vector(s) and the reservoir host(s) of cutaneous leishmaniasis at a study site where active transmission is taking place and where metastasis to the mucocutaneous form of the disease is common. Access to patients in this area provides an opportunity to investigate all aspects of the disease, its treatment or its prevention. We have permanent housing and laboratory space in these areas.

#### PROGRESS

Schistosomiasis. A protocol for primary screening of anti-penetrant agents was initiated to confirm preliminary data generated at the WRAIR schistosomiasis laboratory. Screening of compounds continued under old protocols to detect systemic prophylactic and therapeutic activity. Drug screening was interrupted for several months to allow renovation of mouse colony space and to permit the development of a new colony from brood stock acquired from WRAIR. It was necessary to reestablish mouse rearing facilities at the Núcleo de Medicina Tropical e Nutrição, because the University bioterio was unable to sustain production of the numbers and quality of mice needed. The University of Brasilia has agreed to build a new mouse rearing facility at the Núcleo de Medicina Tropical e Nutrição, specifically to support the schistosomiasis drug screening program.

In the anti-penetrant protocol, 226 compounds were screened and 5 active compounds were detected. In the screen for systemic prophylactic activity 155 compounds were screened. Of these, 13 were found to be toxic and 4 were found to be active by the criteria of the protocol. In the screen for therapeutic activity 92 compounds were screened. None of these were toxic and none of them showed significant activity, according to the criteria of the protocol. These compounds are identified to us only by bottle number. Data are returned to Division of Experimental Therapeutics for analysis and follow-up.

Historically, this program has screened mostly unselected compounds. During the past two years, the

data accumulated over 10 years of screening activity has been entered into a computer at WRAIR and analyzed to detect families of compounds with activity. In the future, compounds to be screened will be selected, using information in this data base. New protocols have been written to optimize data collection from these selected compounds, and computerized transmission of data by satellite from Brazil to WRAIR has been initiated, permitting instantaneous analysis of data and immediate feed-back of data analysis to the Brazil lab.

In the schistosomiasis field study area at Caatinga do Moura, we acquired our first indication of reinfection rate after cessation of an integrated control program that had reduced prevalence from 64% to 19%. In less than a year, prevalence had rebounded to 50%, based on Kato-Katz examinations of single stool samples from 417 people.

Associated with the field study was a clinical study of regression of hepatosplenic diseases in 70 patients given a single treatment with oxamniquine. Reversion of hepatosplenic disease was seen in 40% of the patients after 24 mo. As early as six months after treatment, regression of hepatosplenic disease was seen in 21%. Reversal occurred in four patients that had hepatosplenic disease for over 20 years. This indicated that factors other than age and duration of infection influence the reversibility of hepatosplenomegaly. Results of this study reinforce the concept that, in patients with schistosomal portal hypertension that have not had esophageal bleeding, specific treatment should precede surgical intervention. At least 18 months should be allowed for the effects of treatment to be manifested in observed patients whose condition does not continue to degenerate after treatment.

Ten species of mammals were collected and examined for the presence of Schistosoma mansoni parasites in three endemic areas of the state of Bahia. The prevalence of infection ranged from 67% (30/45) for the wild guinea pig (Cavia aperea) to 11% (3/27) for the field mouse (Akodon sp.). In two sites near Caatinga do Moura, a highly endemic area, 84% (27/32) of the C. aperea examined were infected with S. mansoni parasites before the prevalence in the human population was reduced from 64% to 19% by intensive control measures. None of the 30 C. aperea examined after the control program were infected. This suggests the possibility

that certain species of wild mammals with a very limited home range and which prefer peri-aquatic habitats, such as C. aperea, might be used as indicators of specific transmission sites in endemic areas. These studies will be continued to determine if prevalence of S. mansonii in C. aperea increases in parallel with the demonstrated increase in prevalence in the associated human population after cessation of control measures

Malaria. Studies of malaria in the human population in Costa Marques, Rondônia, continued. Our second dry season survey indicated a prevalence of 9.5% among 451 persons examined in the urban area. Sixty-seven percent of those positive had falciparum malaria. This survey, conducted in the early part of the dry season, indicated double the prevalence rate and double the proportion of falciparum malaria relative to a previous dry season survey. The previous survey involved almost 800 subjects and was conducted in the late dry season. Recent communications from Costa Marques indicate that, as the current rainy season is beginning, malaria transmission is increasing with 25-40 cases per day, mostly falciparum, being seen at the hospital. Our preliminary information suggest a transmission peak during the rainy season, decreasing during the dry season to a minimum just before the rainy season begins. If this can be substantiated, and if it is a regular occurrence, this seasonality will provide an opportunity for intervention by vaccine or prophylactic drug trial.

Demographic data from the most recent survey were added to our demographic data base, which now includes almost 1200 subjects, mostly from the town, as opposed to peri-urban, rural or riverine areas. With the recent opening of a road into Costa Marques, we were able to get a truck there. This ground transportation will permit us to expand our survey activities for both malaria and demographic data to peri-urban and rural areas. Purchase action has been initiated for a boat and motor to permit studies in riverine environments and in remote rubber gathering villages approachable only by boat.

Lack of access during the past rainy season prohibited studies in Costa Marques. A new asphalted landing strip was ready but was not approved for use by the Air Ministry until after the rainy season. Commercial air service, interrupted by the rainy season, has not resumed for economic reasons. However, support

by government aircraft and the opening of the road should allow reliable access during both the rainy and dry seasons. Bus transportation from Porto Velho is presently available, a 15 hr trip of less than 450 miles. Routine surveys are planned during the present rainy season to document the time - pattern of transmission.

Entomological studies in Costa Marques indicated the year round presence of the primary malaria vector Anopheles (Nyssorhynchus) darlingi. An. (Nys.) albitarsis, capable of being an effective malaria vector, is also present year round. Additional potential vectors were found: An. (Nys.) oswaldoi, An. (Nys.) braziliensis, An. (Nys.) triannulatus, An. (Nys.) nuneztovari, An. (Nys.) rondoni and An. (Nys.) matogrossensis, also present, are not known to be vectors.

No known Brazilian malaria vector has been successfully colonized. Attempts to colonize An. darlingi continued, using field collected larvae, adults and ova from both Labrea, Amazonas, and Costa Marques. Two collections from each location, totaling almost 5000 live specimens, were returned to the laboratory for egg collection. These were reared through the larval and pupal stages in the laboratory, and the adults were placed in different sized cages, under different light conditions and with different feeding schedules in unsuccessful efforts to stimulate mating.

Confusion over the identity of some species of the anopheline subgenus Nyssorhynchus, which contains all the known malaria vectors of Brazil, necessitated the initiation of taxonomic studies in cooperation with the Smithsonian Museum, Brazil's Superintendencia for Health Campaigns (SUCAM) and Brazil's National Research Council (CNPq). Funding by WRAIR and CNPq allows the collection of specimens in our field study sites, and eventually others. These are being curated at the Núcleo and prepared for shipment to the Smithsonian Medical Entomology Project. Half of the identified specimens will be returned to the Núcleo and maintained in a museum accessible for teaching and research. Specimens collected at Labrea and Costa Marques, as larvae, are being reared to adults and all skins and adults conserved in associated collections. Study of this material will permit the development of keys for the definitive identification of specimens in field labs and

will help in the resolution of nomenclature problems for species in adjacent parts of South America.

Studies in Labrea to relate vector population changes with progression of the rainy season and the occurrence of malaria continued. Hydrologic data and mosquitoes are collected by a local Núcleo field technician. Malaria data on the local population is provided by SUCAM. Collections in our most productive area, an indian village near town, were suspended from April to June because of an indian uprising that resulted in several killings.

Studies of strain specificity of immunity to falciparum malaria using a microculture growth inhibition assay were continued. Original plans to use only parasites and sera from chronic malaria cases that were immunologically at equilibrium with their malaria proved untenable. A malaria survey in Ariquemes, Rondônia, an area of high malaria transmission, identified only 10 subjects that met these criteria out of 2,950 examined individuals. Because of the low parasitemia in these subjects, only two successful parasite isolates were made. Our present plan is to use sera of long term residents in endemic areas who suffer only mild malaria attacks. Sera of 29 such subjects have been collected. These and other sera will be evaluated against strains of P. falciparum from local and distant areas. We presently have on hand about 150 isolates of P. falciparum and about 500 unassociated sera (which do not necessarily meet the criteria of clinical immunity). Two strains of malaria to be used as controls have been characterized in cultures in the laboratory.

Studies on the development of partial immunity to malaria in relation to duration of residency in an endemic area are underway at Ariquemes. This area has recently undergone a period of intense development with a large population influx. A 1984 malaria survey indicated a malaria prevalence of 11.6%, with 64% P. falciparum. Malaria was most prevalent in peri-urban areas (24% of infections) followed by rural (11%) and urban areas (2%). A 1985 survey in the same area indicated a prevalence of only 1.6%, with predominance of P. vivax. Insufficient epidemiological and demographic data are available to explain these differences. Preliminary clinical and epidemiological data suggest that both the frequency and intensity of

malaria attacks vary inversely with duration of residency in an endemic area. A decrease in prevalence and severity of malaria was observed in individuals living for over three years in this area of malaria transmission.

Leishmaniasis. Studies to determine the wild mammal reservoir host of L. b. braziliensis continued in Três Braços and Corte de Pedra, Bahia, areas of active transmission to humans. Trapped wild animals were necropsied in field laboratories and blood, sera and impression smears were taken. Tissue specimens (skin, liver and spleen) were inoculated into hamsters, and the hamsters were taken to Brasília for observation.

In the Três Braços and Corte de Pedra areas, 68 nights of trapping (4,681 trap nights) in tall forest, secondary forest, secondary scrub, orchards, cropland and peridomestic habitats yielded 234 mammals of 19 species. Tissues from 212 mammals were inoculated into hamsters, impression smears of liver and spleen were made from 216, sera were recovered from 134 and isolations in culture media were attempted from 13. To date, 1059 animals of 30 species have been captured and examined in this area.

Four additional isolates of a subspecies of L. mexicana were made from the spiny rat (Proechimys inheringi denigratus), bringing the total to seven isolates. They were determined by isoenzyme studies to be closely related to L. b. amazonensis but differ by decreased electrophoretic mobility of GPI, ALAT and PEP. They are distinguishable also from L. mexicana subspecies from the state of Goiás, L. m. mexicana, L. m. pifanoi, L. m. garnhami and L. m. aristedesii. This species of rodent prefers the tall forest habitat and only rarely has been captured in the secondary forest.

Arthropod ectoparasites were collected from all specimens and sent to specialists. Clippings of fur were taken for fungal isolations in a cooperative study with the University of Brasília. Mammalian study materials were preserved for our study of mammals of the Brazilian coastal forest in cooperation with the Division of Mammals, Smithsonian Institution.

A new health post, in which we will have laboratory space, is scheduled for construction in Corte de Pedra by the local government. Improved laboratory facilities

as well as lodging will then be available to us in both Três Braços and Corte de Pedra.

In studies to determine the vector of L. b. braziliensis in Corte de Pedra and Três Braços, Bahia, areas of active transmission to humans, approximately 500 individual sand fly collections have been made from various habitats utilizing a variety of collecting techniques. Over 22 sand fly species have been identified. Lutzomyia (Lu.) whitmani and Lu. intermedia are notably the most abundant species collected in the peri-domestic and domestic habitats. Lu. whitmani has been implicated as a potential vector for human leishmaniasis due to its man biting behavior and relative abundance in domestic and peri-domestic habitats. Laboratory and field studies have demonstrated that this sand fly species is capable of being infected with the L. b. braziliensis strain of leishmaniasis. In other regions of Brazil (Rio de Janeiro and São Paulo State) Lu. intermedia has been found naturally infected with L. b. braziliensis. However, transmission studies to confirm its vectorial capacity are lacking. It is important that Lu. migonei is also being collected in and near the houses in the highly endemic study sites of Bahia. This sand fly species has been found in other area to be infected with various forms of non-identified flagellate parasites, which could have been L. b. braziliensis.

Over 8,000 wild caught sand flies representing some 22 species from leishmanial endemic areas have been identified and dissected for leishmanial parasites.

Thus far four species of sand flies Lu. whitmani, Lu. sp. (Subgenus: Barrettomyia), Lu. schreiberi and Lu. intermedia, have been found naturally infected with flagellate parasites. Slide mounted samples of the parasites indicate notably different morphological characteristics, strongly suggesting four different strains of flagellate parasites. All sand fly parasites were inoculated into Difco modified blood agar medium. Parasites obtained from Lu. whitmani, Lu. schreiberi and Lu. spp. (Barrettomyia) were also inoculated into hamsters. None of the inoculated hamster have demonstrated signs of infection. The only parasite to be established in the modified blood culture media was from a single L. whitmani. Even though characterization of this parasite is incomplete, it is evident that it is not of genus Leishmania. These findings demonstrate

that various species of sand flies collected in leishmania endemic areas may harbor a variety of non-leishmania flagellate parasites. Thus, it is imperative to isolate, cultivate and identify sand fly borne parasites prior to their being considered human leishmania parasites.

Efforts are being made to establish colonies of potential vectors of leishmania, ie., Lu. whitmani and Lu. intermedia. The former sand fly species has been successfully maintained in the laboratory up to 3-4 generations. However, because so few adults are produced, it is lost in subsequent generations. An attempt to colonize Lu. intermedia was only recently initiated. Eggs from blood fed, field collected adults were collected in the laboratory and the resulting larvae are developing well. Successful colonization of these two sand fly species will enable us to determine their vector potential in the laboratory and to conduct basic biological and ecological studies in the field.

#### RECOMMENDATIONS:

1. Assign a physician-epidemiologist to USAMRU, Brasilia to optimize the opportunities we have for epidemiological research.
2. Assign a parasitologist to USAMRU, Brasilia to supervise the schistosomiasis drug screening program and to develop opportunities for field schistosomiasis research.
3. Assign an administrative NCO to USAMRU, Brasilia to relieve the professional staff of routine administrative burden.
4. Computerize all data bases.
5. Implement WRAIR computerized purchasing and accounting procedures to minimize book keeping.
6. Concentrate malaria epidemiology studies in Costa Marques and initiate survey of anti-sporozoite antibody prevalence.
7. Acquire and use mono-clonal antibody technology to detect malaria infected mosquitoes and to identify the malaria species.

8. Close-out mosquito studies in Lábrea, Amazonas.
9. Conduct serological tests on sera taken from mammals in the leishmania reservoir host study. Although positive results may be due to interaction with Trypanosoma infections, consistent negative results for some of the species which are collected in high numbers would aid in selecting certain species for intensive laboratory tests and cultures and in determining which collecting procedures to use.
10. Employ the technique of Grimaldi, et al. 1984. (Trans. R. Soc. Trop. Med. Hyg., 78:560) in which 5-7 days after inoculating hamsters with tissue taken from the wild mammals, tissue is excised from the site of inoculation, and placed in culture medium. Inoculation of culture media may then be conducted in the Brasilia laboratory under sterile conditions, instead of attempting to culture the parasite in the field.
11. Do experiments to determine the optimum time at which to examine hamsters for Leishmania parasites after they have been inoculated with tissue from mammals collected in the field.

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- Hoch, A.L. 1985. Review of some tropical diseases transmitted by insects. Curso de Especialização em Medicina Tropical. Faculdade de Medicina, Universidade de Brasília. 2 Sep - 26 Oct.
- Peterson, N.E. 1985. Mammalogical aspects of tropical medicine. X Curso de Aperfeiçoamento em Medicina Tropical. Faculdade de Medicina, Universidade de Brasília. 2 Set - 26 Out.

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Dietze, R. and A. Prata. Rate of regression of hepatosplenic schistosomiasis after specific therapy.

Hoch, A.L., F.P. Pinheiro, D.R. Roberts and M.L.C. Gomes. Oropouche: Laboratory transmission by Culex quinquefasciatus Say.

Hoch, A.L., D.R. Roberts and F.P. Pinheiro. Breeding sites of Culicoides paraensis.